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Allergic reactions in endodontic practice

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Introduction

Endodontic practice includes surgical and medicinal therapy of inflamed and/or infected tissues through a narrow and leaky dentinal peephole that eventually has to be tightly sealed in all directions. Therapeutic conditions of this nature require the use of a series of remedies and biomaterials with varying degrees of temporary or permanent soft tissue contact, such as

- barrier equipment, i.e. dams and gloves,
- disinfectants for the external part of the tooth and the adjacent area,
- washing, cleansing, and disinfectant fluids for root canals,
- temporary antibacterial pastes and temporary filling materials,
- permanent sealers and core materials,
- apical filling materials,
- permanent restoration materials,
- antibiotics.

All groups contain allergens (Table 1).

The purpose of the present paper is to identify potential allergens and review reports on materials/remedies related adverse effects of allergic nature. Mechanisms of allergic reactions are summarized as a background in the discussion of materials related allergy vs. innate immunological reactions or other inflammatory defence mechanisms. Allergic reactions associated with antibiotics or permanent restorative materials are not included.

Mechanism of allergic reactions

Sensitization and allergic reactions

Allergic reactions depend on the individual's genetic disposition and previous exposure to the allergen (sensitization). Exposure routes comprise skin, mucous membranes, alimentary tract, or lungs. In addition, parenteral exposure is a possibility for implanted medical devices. The allergic reactions following parenteral exposure is sometimes called 'systemic' allergy. The parenteral nature of endodontic fillings resemble that of implants.

Materials related reactions could be cell mediated, delayed reactions (Type IV) or immediate reactions with humoral antibodies (Types I–III). The delayed reactions are characterized by different forms of allergic contact dermatitis or mucositis, in which T lymphocytes, custom made for the particular allergen, act in concert with other lymphocytes and mononuclear phagocytes to cause swelling, induration or eczema. The latter reaction form of delayed hypersensitivity has been of specific importance in relation to biomaterials.

The immediate reactions are based on the encounter between the intruding allergen and existing antibodies released by mast cells. Types II and III, comprising complement activation, cell lysis, and release of vasoactive substances, have been essentially excluded from biomaterials discussion, leaving Type I, characterized by reactions such as asthmatic seizures, swelling of the mucosa of the throat, anaphylaxis, or urticaria. Type I reactions are based on the release of active mediators by interaction between the IgE immunoglobulin in mast cells, eosinophils, and platelets and the intruding allergen.

The Type I reactions are traditionally associated with full antigens. With the exception of residual plant protein in natural rubber latex (NRL), potential allergens in endodontics are haptens, turning full antigens only after combination with host tissue proteins on macrophages and Langerhans cells. However, new information has shown that Type I reactions

Table 1. Some current materials and remedies in endodontics and their allergenic potential (9–12)

Area of application	Chemical group	Allergenic potential
Barrier equipment	Natural rubber latex	+
	Residual proteins and chemical additives	+
	Polyisoprene	–
Surface disinfectants	Hydrogen peroxide (30%)	–
	Tincture of iodine (5%)	+
	Chlorhexidine (0.5%)	+
Disinfectants for root canals	Phenol and derivatives	+
	Aldehydes	+
	Potassium iodide (2%)	–
	Benzalkonium chloride (0.1–1.0%)	+
	Chloramine	+
	Sodium hypochlorite (Dakin's solution, 0.5–1.0%)	+
Temporary antibacterial paste	Calcium hydroxide	–
Temporary filling materials	ZnOE and ZnOE modified with alumina, natural resin, or PMMA	+
Sealers	Chloroform, for chloropercha (earlier)	–
	Salicylate, with calcium hydroxide	–
	ZnOE formulas with thymol, Peru balsam, colophony, formaldehyde releasing pastes (Endomethazone, N2)	+
	Polyketone liquid with ZnO containing 0.5% dichlorophene	+
	Epoxy resin, with bismuth, tetraamine, silver, titanium dioxide in bisphenol-A-diglycidylether monomer (AH26, AHPlus)	+
	Glass ionomers	–
Core materials	Gutta-percha. Natural 1,4-isoprene polymer	?
	Silver	+
Apical filling materials	Amalgam	–
	Glass ionomers	–
	Calcium chelate/polyvinyl resin (Diaket)	–
	Mineral trioxide aggeregates	–
	Gutta percha	?
	ZnOE	+
	Composite resins	+

may also be elicited by haptenic substances, such as metal ions (1), leaving the border between cell mediated delayed reactions and immediate humoral reaction less simple.

Implant allergy, a parallel to endodontics?

Case reports indicate that loosening or other dysfunction of metallic implants may be related to Type IV metal allergy (2) or allergy to components in the bone cement (3), as revealed by patch tests. These reactions are sometimes accompanied by allergic contact dermatitis and urticara and are considered to be the result of previous sensitization, although the opposite mechanism has not been excluded from the discussion: metal sensitization by grinding parts of a loosening implant (4). The observed allergic side effects in endodontics are similar dermal reactions and, as has been speculated, local tissue reactions inhibiting apical healing (5).

Allergen exposure conditions

Allergic reactions require contact with host tissue cells outside the mineralized dentine, able to supplement the haptens with specific proteins, and to provide transport to immunocompetent organs. The direct soft tissue contact is limited to the tooth apex or accessory root canals, imparting strict quantitative limitations, although retrograde filling or apical overfill increase the contact area considerably. In addition, passage of solutes through dentinal tubules cannot be disregarded during debridement procedures and by leakage from the endodontic filling (6). *In vitro* experiments have shown that dentinal tubules are pathways for liquid transport, an intact and well-mineralized acellular root cement probably representing an important barrier *in vivo*.

However, the anatomical structure in the apical region shows marked variations such as irregular primary tubules and accessory root canals (7), representing a challenge during endodontic therapy as well as increasing the possibility of soft tissue exposure for potential allergens. The cellular and less mineralized cement located to this part of the tooth probably does not represent a barrier. For similar reasons the furcature region of multirooted teeth should not be overlooked. Moreover, the 'on site' production of the endodontic filling renders an amorphous product different from prefabricated implants with regard to physical structure and surface characteristics. Surface characteristics are important for the bioreaction of all implant materials (8), and the rough surface of the endodontic implant facilitates degradation and leakage of material components.

In summary, minute quantities of chemical substances associated with endodontic therapy may establish contact with immunocompetent host tissue, particularly in the apical region. It is unclear whether dentinal transport of allergen-containing chemicals results in soft tissue contact *in vivo*. Inadvertent mucosal exposure and inhalation of volatile fluids are contact possibilities outside the apical/dentinal area.

Potential allergens in endodontics

Table 1 summarizes main endodontic materials and medicaments on the basis of current teaching in the Scandinavian countries (9–11). A majority of the ingredients are adaptations of substances used in general dentistry or medicine. Their allergenic potential is based on empirical information from case reports and from animal experiments (12, 13). One characteristic difference as compared with general dentistry, is the absence of metal alloys containing nickel, gold, chromium or cobalt comprising a majority of the allergic reactions (14). Excluding endodontic instruments, metal alloys are limited to silver core materials and amalgam for retrograde filling. In addition, heavy metal salts may be present in sealer or core materials for radioopacity purposes.

Barrier equipment

Good endodontic practice requires strict demands for isolation and disinfection of the oral working environment. NRL in dams or gloves contains allergens of different types. Of these, residual latex proteins may elicit immediate IgE based reactions, affecting throat and airways or giving anaphylactic symptoms in sensitized individuals. In addition, chemicals from the production process may act as haptens and give delayed dermal or mucosal reactions (15).

Disinfectants and antibacterials

Tincture of iodine and chlorhexidine are potential haptens, but allergic reactions are uncommon, particularly for chlorhexidine, although long-term, repeated

ulcer treatment has given immediate reactions (12). Classical antimicrobials such as camphorated phenols, formocresol, and cresatin are all allergenic substances, together with formaldehyde, but are now replaced by the quaternary ammonium compound benzalconium choride, or chloramine. These compounds are rare sensitizers, although a moderate sensitizer, chloramine may produce immediate contact reactions. Allergic reactions associated with sodium hypochlorite (modified Dakins solution) are uncommon, but have been reported (16). The surface disinfectant hydrogen peroxide and the temporary antibacterial paste calcium hydroxide are not allergenic remedies.

Temporary filling materials

Temporary filling materials are included in the present survey for two reasons: their content of recognized sensitizers and their possibility of mucosal contact after barrier removal. Eugenol is allergenic, temporary ZnOE formulations being responsible for 1/6 of perceived side effects in prosthodontics (17). Natural resins, such as colophony, and methacrylate monomers are also allergens.

Sealers

The organic solvent chloroform used earlier with gutta-percha (chloropercha) is irritant and toxic, but allergic reactions are not seen. Salicylate with calcium hydroxide is also inert, whereas the group of sealers made up of ZnOE supplemented with Peru balsam, colophony, or thymol is a composite of recognized allergens. Formaldehyde released by Endometazone and N2 in this group of sealers adds to their allergenic potential.

Polyketone sealers, based on propionylactophenone monomer chelating with Zn in ZnO contains some dichlorophene, which is allergenic. Epoxy-resin sealers are based on the allergenic bisphenol A-diglycidylether (badge) and may contain silver, bismuth and titanium dioxide, but releases less formaldehyde than the ZnOE sealers. Glass ionomers are not allergenic.

Core materials and apical filling materials

In principle, silver ions are allergens. Silver cones as core material are subject to corrosive reactions, but allergic reactions have not been reported. Gutta-percha is still the preferred core material because of its physical and chemical characteristics. The natural gutta-percha is a 1,4-isoprene polymer available in α and β forms. The β form is used in the cones together with ZnO and barium sulphates for radioopacity. Other additives are pigments and colophony. Gutta-percha is considered non-allergenic. However, cross-reaction with NRL has been suggested (see below).

The apical filling materials include traditional items such as amalgam, gutta-percha, and ZnOE cements modified with alumina and resins. In addition, glassionomers, ZnO/calcium sulphate, calcium chelate/polyvinyl resin or mineral trioxide aggregates are used. Other retrograde filling materials contain methacrylates such as BISGMA/TEGDMA. ZnOE cements and resin-based materials in this group are well-known allergens.

General comments on potential allergens

The stock of substances in endodontic practice changes with the development of new materials and discarding of old. Devitalizing agents containing arsenic, phenol, or cocaine etc. have been discarded together with old filling materials such as asphalt, phenols, creosote and others. Many of these substances had their parallels in industry and represented an allergenic as well as an environmental hazard. Revising the endodontic armamentarium is not a synchronized activity. The selection of ingredients presented in Table 1 is therefore a composite of new and old items, most of them being allergens.

To our knowledge, there are no prevalence studies aimed specifically at allergic reactions in endodontic practice. Questionnaire studies on adverse reactions associated in other branches of dentistry have indicated a maximum frequency of 1 in 300 orthodontic patients, including allergic as well as irritative reactions (18). This has been explained by the use of base-metal alloys and by the dermal exposure of extraoral appliances in addition to the mucosal exposure. It is accepted that dermal exposure, particularly to metallic allergens, is more likely to elicit allergic reactions than, e.g. the mucosal exposure. The prevalence of allergic reactions in endodontics is assumed to be considerably lower. A possible explanation could be that the exposure area is small and limited to the parenteral route and that the strongly allergenic metal ions are absent. On the other hand, antibacterial remedies in the root canal represent an exposure mode for potential allergens not associated

with other dental treatment. This fact is reflected in case reports on allergic reactions.

Case reports and experiences

As indicated above, endodontic practice includes the application of allergens in several steps of the treatment procedure. Since substances in dental materials are not exclusive to dentistry, a certain percentage of patients undergoing endodontic therapy will have an acquired allergy for one or more of these substances. The majority of case reports on this subject are concerned with the use of formaldehyde in disinfectants or devitalizing pastes. Other reports include reactions to epoxy or other resin-based materials in root-canal sealers or in retrograde fillings, or reactions associated with NRL as barrier equipment. In addition, some authors discuss the possibility of cross-reactions between NRL-factors and the chemically similar gutta-percha.

Formaldehyde

Formaldehyde (formol, formalin, trioxymethylene) is a recognized allergen able to provoke gastroenteric, respiratory and dermatological reactions. Immediate reactions in the form of rhinitis, asthma, urticaria, and anaphylaxis are also seen. A 57-year-old male developed a generalized itchy skin rash and intense facial swelling after application of endomethasone, which contains paraformaldehyde. X-rays showed apical overfill. An allergic etiology was suspected on the basis of anamnestic information, but patch test proved negative (19).

A 41-year-old male patient, undergoing endodontic treatment in the form of debridement of an infected root canal and placement of a sealer, experienced a life threatening anaphylactic reaction (20). Allergy tests revealed a strong positive reaction to the formol part of the sealer, with increased IgE plasma concentration. It was argued that a considerable apical overfill initiated the reaction.

Kunisada et al. (21) described wheal and flare of the entire body combined with systemic symptoms such as wheesing, cough, dyspnoea in a 50-year-old woman, who was subjected to endodontic treatment with a disinfectant containing paraformaldehyde. Diagnostic tests indicated IgE dependent immediate reactions, as well as delayed reactions. These authors also analyzed 15 other published cases of anaphylaxis and urticaria following root-canal treatment with a formaldehyde disinfectant, about half of which showed positive patch tests. Braun et al. (22) later reported anaphylactic shock in four endodontic patients, and generalized urticaria in three others associated with formaldehyde. Their review contained 36 cases, partly overlapping the previous authors.

On the basis of these reports, it is fairly well established that formaldehyde may lead to allergic reactions after endodontic treatment. The reaction pattern indicates an immediate type of allergy, although delayed reaction could not be excluded. According to Braun et al. (22) the delayed reactions could be explained by continued leakage of formaldehyde through dentinal tubules or from an apical overfill. Patch tests were inconclusive.

Epoxy and other resins

An early observation of epoxy allergy was published in 1976, describing a reaction to the endodontic material AH26, giving pain in the apical area, accompanied by facial erythema after repeated endodontic treatment (23). Patch tests indicated that the liquid ingredient, i.e., the bisphenolglycidyl ether, is the allergen. Another report described mental nerve paresthesia caused by direct pulp capping with a HEMA- and TEGDMA-based restorative system. Patch tests revealed contact dermatitis for several methacrylates. It was speculated that sensitization could have taken place by repeated previous dental treatment (24). However, large clinical studies by Danish authors with dentine bonding composite resins as root end sealant have not indicated allergic responses in cases of failed healing (25, 26).

Sodium hypochlorite

Sodium hypochlorite allergy among dental patients may occur following previous contact with household bleach (27). 'Non-allergic hypersensitivity' to the hypochlorite is another possibility (28). Allergic reactions after root canal irrigation have been reported (29), but more concern has been expressed for other complications after inadvertent injection of sodium hypochlorite into apical tissue (30).

NRL and gutta-percha

Similar to other branches of dentistry, allergic contact dermatitis due to NRL in dams or gloves are seen among

endodontic patients. In addition, case reports indicate allergic reactions of Type I after treatment of patients who were hypersensitive to NRL using the gutta-percha/chlororform technique (31, 32). Persisting discomfort and urticarial symptoms necessitated removal of the root fillings after which the symptoms resolved. Cutaneous tests showed an extreme irritant reaction to gutta-percha dissolved in chloroform (32). It was argued that the phenomenon could be explained by a cross-reaction between the NRL-product of the Hevea brasiliensis tree (cis-1,4-polyisoprene) and the gutta-percha (trans-1,4-polyisoprene) of the Palaquium tree.

However, commercial products of NRL and gutta-percha are both subject to many steps of chemical treatment leaving residual chemicals and not only residual plant proteins. Moreover, the gutta-percha cones contain zinc oxide, heavy-metal sulphates, waxes, resins and pigments. Attempts to demonstrate cross-reactions between commercial gutta-percha and NRL products by advanced immunological laboratory methods have not been successful (33), although there were indications that raw gutta-percha and raw NRL may show some cross-reactivity. This is similar to the fact that antibodies to chitinases of ficus plants, avocados and bananas may be present in patients with Type I allergy to NRL.

In summary, although gutta-percha is not considered a liability in endodontic practice, it is advised to be aware of the increased possibility of allergic reactions to materials and remedies among patients with multiple allergies, including NRL allergy.

Allergic sensitization by endodontic treatment?

Case reports followed by immunological testing showed that allergic reactions following endodontic procedures may take place among previously sensitized patients. However, could patients be sensitized by endodontic treatment? Braun et al. (22) present interesting arguments for the possibility of sensitization to formaldehyde by repeated endodontic treatment, on the basis of contact with immunocompetent tissues in the adjacent apical region. However, valid evidence for sensitization beyond clinical observations has been difficult to provide.

Attempts to find experimental evidence have indicated an altered immunologic response to sealers in root fillings after primary immunization by injection of sealer/pulp tissue extracts into dogs' lymph nodes (34). This rationale was based on the assumption that sealer haptens combine with residual pulp tissue proteins to form allergens. The reactions to positive control experiments, placing sheep erythrocytes (recognized antigens) in empty pulp chambers, was interpreted as evidence of the ability of eliciting immunologic reactions via the root canal, but did not really provide evidence for primary sensitization by this route. These observations are in accordance with information from early investigations showing no positive patch tests to strong antigens such as formaldehyde, cresol, and eugenol in children after multiple formocresol pulpotomized primary teeth (35). A fair attitude to this question at the present time is that sensitization of the non-allergic patient by the endodontic material is unlikely, whereas an overt reaction in a previously sensitized individual is possible.

Concluding remarks

Endodontic practice includes short-time application of a series of allergenic chemicals, and permanent placement of *in situ* produced implants with physical properties liable to dissolution and leakage. As in other branches of dentistry, a certain percentage of patients will be sensitized to one or more of these ingredients, which are often present in other products of everyday life. The apparently low prevalence of adverse effects associated with endodontic practice could be explained by three factors: the small apical exposure area, the limited possibility for passage through dentine, and the absence of important allergens characteristic of general dentistry, such as metal ions.

The most frequent and most severe reactions have been observed after application of strong, water-soluble allergens such as formaldehyde and sodium hypochlorite, but allergic reactions to methacrylate sealers have also been observed. The case reports indicate that both immediate and delayed immune reactions may take place. Proven allergic reactions have been systemic, i.e. giving allergic symptoms unrelated to the exposure site. Suspected local reactions in the form of failing endodontic therapy, similar to implant failure, have been difficult to prove and must be characterized as a still unresolved question.

Understandable concern has been paid to the possibility of cross-reaction between NRL and the core

material gutta-percha, because NRL allergy is fairly common. Although there is no direct immunological evidence of a real cross-reaction between commercial products derived from these sources, a series of residual allergens associated with the production process may have common components. It is therefore wise to take all precautions in endodontic treatment of such patients. In general, clarification of existing allergies is important in endodontics as in other branches of surgical interventions.

In conclusion, endodontics represent an important part of dental therapy with very limited risk of provoking allergic reactions associated with materials and remedies, although many ingredients are classified as allergens.

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